

Clinical Trial Protocol: VISTA-1 / 18-110-0004

Protocol Title: A Phase 3, Multi-Center, Randomized, Double-Masked, Placebo-Controlled Clinical Study to Assess the Safety and Efficacy of SkQ1 Ophthalmic Solution in the Environment and During Challenge in the Controlled Adverse Environmental (CAE[®]) Model for the Treatment of Dry Eye Syndrome

Protocol Number: VISTA-1 / 18-110-0004

Study Phase: 3

Product Name: SkQ1 Ophthalmic Solution

IND Number: 113433

Indication: Dry Eye Syndrome (DES)

Investigators: Multi-Center

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SPONSOR PERSONNEL

[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]


ORA PERSONNEL


[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]

SYNOPSIS

Protocol Title:	A Phase 3, Multi-Center, Randomized, Double-Masked, Placebo-Controlled Clinical Study to Assess the Safety and Efficacy of SkQ1 Ophthalmic Solution in the Environment and During Challenge in the Controlled Adverse Environmental (CAE [®]) Model for the Treatment of Dry Eye Syndrome
Protocol Number:	VISTA-1 / 18-110-0004
Study Drug:	1) 0.155 µg/mL SkQ1 ophthalmic solution 2) 1.55 µg/mL SkQ1 ophthalmic solution 3) Placebo SkQ1 ophthalmic solution (Vehicle of SkQ1 ophthalmic solution)
Study Phase:	3
Study Objective:	The objective of this study is to compare the safety and efficacy of SkQ1 ophthalmic solution to placebo for the treatment of the signs and symptoms of dry eye syndrome.
<u>Overall Study Design</u>	
Structure:	Multi-center, double-masked, randomized, placebo-controlled study
Duration:	An individual subject's participation is estimated to be approximately 9 weeks (63 days)
Controls:	Placebo SkQ1 ophthalmic solution (Vehicle of SkQ1 ophthalmic solution)
Dosage/Dose Regimen:	Subjects eligible to be randomized will receive one of the following treatments to be administered bilaterally 1-2 drops ■■■ for 56 days (from Visit 2 to Visit 5). 1) 0.155 µg/mL SkQ1 ophthalmic solution 2) 1.55 µg/mL SkQ1 ophthalmic solution 3) Placebo SkQ1 ophthalmic solution (Vehicle) During a 7-day study run-in period (beginning at the end of Visit 1 for the purpose of subject selection) prior to randomization, all subjects will receive 1-2 drops of Placebo SkQ1 ophthalmic solution (Vehicle) bilaterally ■■■
Summary of Visit Schedule:	5 visits over the course of approximately 9 weeks <ul style="list-style-type: none"> • Visit 1 = Day -7 ± 1 day, Environmental Screening • Visit 2 = Day 1, Baseline, Environmental Screening Confirmation, Randomization and Initiation of Double-Masked Treatment

	<ul style="list-style-type: none"> • Visit 3 = Day 29 ± 2 days • Visit 4 = Day 43 ± 2 days • Visit 5 = Day 57 ± 4 days, 8-Week CAE® Test, End of Double-Masked Treatment
Measures Taken to Reduce Bias:	This is a double-masked study.
<u>Study Population Characteristics</u>	
Number of Subjects:	Approximately [REDACTED] subjects will be screened to enroll approximately 444 (148 low dose: 148 high dose: 148 placebo) subjects
Condition/Disease:	Dry Eye Syndrome
Inclusion Criteria:	<p>Subjects must:</p> <ul style="list-style-type: none"> a. Be at least 18 years of age; b. Provide written informed consent; c. Have a subject reported history of dry eye for at least 6 months prior to Visit 1; d. Have a history of use or desire to use eye drops for dry eye symptoms within 6 months of Visit 1; e. [REDACTED] f. [REDACTED] g. [REDACTED] h. [REDACTED] i. [REDACTED]

	<p>j. </p> <p>k. Have at least one eye (the same eye) satisfy all criteria for f, g, h, i, and j above.</p>
Exclusion Criteria:	<p>Subjects must <u>not</u>:</p> <ul style="list-style-type: none"> a. Have participated in the previous SkQ1 ophthalmic solution Phase 2 treatment study; b. Have any clinically significant slit lamp findings at Visit 1 that may include active blepharitis, meibomian gland dysfunction (MGD), lid margin inflammation or active ocular allergies that require therapeutic treatment, and/or in the opinion of the investigator may interfere with study parameters; c. Be diagnosed with an ongoing ocular infection (bacterial, viral, or fungal), or active ocular inflammation (e.g. follicular conjunctivitis) at Visit 1; d. Have worn contact lenses within 7 days of Visit 1 or anticipate using contact lenses during the study; e. Have used any eye drops within 2 hours of Visit 1; f. Have previously had laser-assisted <i>in situ</i> keratomileusis (LASIK) surgery within the last 12 months; g. Have used Restasis[®], Xiidra[®] or CEQUA[™] within 60 days of Visit 1; h. Have had any ocular and/or lid surgeries within 6 months of Visit 1 or any planned over the study period; i. Be using or anticipate using temporary punctal plugs during the study that have not been stable within 30 days of Visit 1; j. Be currently taking any topical ophthalmic prescription (including medications for

	<p>glaucoma) or over-the-counter (OTC) solutions, artificial tears, gels or scrubs, and cannot discontinue these medications for the duration of the trial (excluding medications allowed for the conduct of the study);</p> <p>k. Have corrected visual acuity greater than or equal to logMAR+0.7 as assessed by Early Treatment of Diabetic Retinopathy Study (ETDRS) scale in both eyes at Visit 1;</p> <p>l. Have an uncontrolled systemic disease;</p> <p>m. Be a woman who is pregnant, nursing or planning a pregnancy;</p> <p>n. Be unwilling to submit a urine pregnancy test at Visit 1 and Visit 5 (or early termination visit) if of childbearing potential. Non-childbearing potential is defined as a woman who is permanently sterilized (e.g. has had a hysterectomy or bilateral tubal ligation or bilateral oophorectomy), or is post-menopausal (without menses for 12 consecutive months);</p> <p>o. Be a woman of childbearing potential who is not using an acceptable means of birth control; acceptable methods of contraception include: hormonal – oral, implantable, injectable, or transdermal contraceptives; mechanical – spermicide in conjunction with a barrier such as a diaphragm or condom; IUD; or surgical sterilization of partner. For non-sexually active females, abstinence may be regarded as an adequate method of birth control; however, if the subject becomes sexually active during the study, she must agree to use adequate birth control as defined above for the remainder of the study;</p> <p>p. </p> <p>q. Have a condition or be in a situation which the investigator feels may put the subject at</p>
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	<p>significant risk, may confound the study results, or may interfere significantly with the subject's participation in the study;</p> <p>r. Be currently enrolled in an investigational drug or device study or have used an investigational drug or device within 30 days of Visit 1;</p> <p>s. Be currently using any medication known to cause ocular drying that is not used on a stable dosing regimen for at least 30 days prior to Visit 1;</p> <p>t. Be currently using any hormone replacement therapy that is not used on a stable dosing regimen for at least 30 days prior to Visit 1 and during the study;</p> <p>u. Be unable or unwilling to follow instructions, including participation in all study assessments and visits.</p>
Study Formulations and Formulation Numbers:	<p><u>Run-in:</u> Placebo to be supplied by the sponsor.</p> <p><u>Study Drug:</u> Batch/lot information for SkQ1 ophthalmic solution (0.155µg/mL, 1.55µg/mL and Placebo) to be supplied by the sponsor.</p>
<u>Evaluation Criteria</u>	
Efficacy Measures:	<p><u>Primary Efficacy Measures:</u> The following primary endpoint will be tested:</p> <ul style="list-style-type: none"> Change from baseline (Visit 2) in Corneal fluorescein staining in the central region at Visit 5 (Day 57) [REDACTED] Change from baseline (Visit 2) in Grittiness at Visit 5 (Day 57) [REDACTED] <p><u>Secondary Efficacy Measures:</u></p> <ul style="list-style-type: none"> [REDACTED]

	<div style="background-color: black; width: 100%; height: 100%;"></div>
Safety Measures:	<ul style="list-style-type: none"> • Visual acuity (ETDRS); • Slit-lamp biomicroscopy; • Adverse event query; • Dilated fundoscopy • Intraocular pressure
Other:	<ul style="list-style-type: none"> • <div style="background-color: black; width: 100%; height: 1em;"></div>
General Statistical Methods and Types of Analyses <u>Analysis Populations</u> <ul style="list-style-type: none"> • <u>Intent-to-Treat Population</u> – The intent-to-treat (ITT) population includes all randomized subjects. The primary and secondary efficacy analyses will be performed on the ITT population. Subjects in the ITT population will be analyzed as randomized. • <u>Per-Protocol Population</u> – The per-protocol (PP) population excludes subjects with significant protocol deviations or who do not complete the study. Protocol deviations will be assessed prior to database lock and unmasking. Subjects in 	

the PP population will be analyzed as treated.

- Safety Population – The safety population will include all subjects receiving treatment from whom at least one safety measurement is obtained following the first dose of study drug. The safety population will be analyzed for all safety assessments. Subjects in the Safety population will be analyzed as treated.

Sample Size

To address the multiple primary efficacy variables employed in this study, the sample size calculations have been based on a hierarchical structure. In order to test a variable, the preceding variable(s) must have shown statistically significant improvements versus placebo using a two-sided significance level of 0.05. Using these strategies, the Type I error rate will be maintained at the 0.05 significance level for the primary efficacy variables.

This study is expected to enroll 148 subjects in the active treatment arms and 148 subjects in the placebo group [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED], enrollment of 148 patients per group would be required for 90% power to detect the differences between each active group and placebo.

Primary Efficacy Analyses

Efficacy analyses will be performed on the ITT population. Supportive analyses will be performed on the PP population.

Primary efficacy endpoints are:

- Change from baseline (Visit 2) in Corneal fluorescein staining in the central region in the worst eye at baseline: [REDACTED] at Visit 5

- Change from baseline (Visit 2) Grittiness: [REDACTED] at Visit 5

The primary efficacy endpoints will be analyzed using an analysis of covariance (ANCOVA) [REDACTED]

[REDACTED] he adjusted least squares means and their standard errors (SEs) will be presented along with their two-sided 95% confidence intervals (CIs) for each treatment group and the difference between the active treatment group and the placebo treatment group. In addition, a two-sample t-test and Wilcoxon rank sum test will be used to compare the active and placebo groups in the change from baseline at Visit 5 [REDACTED]. The mean difference, SD for the difference, and the 95% CI for the difference will be presented. A two-sided p-value < 0.05 will be considered statistically significant.

The primary analyses for both primary endpoints will be conducted on the ITT population using the Markov Chain Monte Carlo (MCMC) multiple imputation method to impute missing data. [REDACTED]

[REDACTED] ensitivity analyses will also be performed using Last Observation Carried Forward (LOCF) method on the ITT population as well as with the observed data only for both ITT and PP populations.

Secondary Efficacy Analyses

Secondary efficacy variables will generally be analyzed on the ITT population using observed data. Imputation will not be applied for any missing data in the secondary efficacy endpoints.

Analyses will use two-sample t-tests, Wilcoxon rank sum tests (for count or rank-based data, including symptom scores at individual time points), and ANCOVA models with baseline values included as covariates where appropriate. [REDACTED]

Safety Variables

Frequencies and percentages of subjects with treatment-emergent adverse events (TEAEs), serious TEAEs, and TEAEs causing premature treatment discontinuation will be provided by treatment group. An AE is treatment emergent if it occurs or worsens after the first dose of study treatment. Furthermore, frequencies will be given of subjects with TEAEs by system organ class and preferred term for the following categories of AEs:

- All TEAEs
- TEAEs at least possibly related to study treatment
- TEAEs leading to study treatment discontinuation
- Serious TEAEs

- By maximal severity
- By study day of onset

Separate analyses will be performed for ocular and non-ocular AEs.

Other safety endpoints will be summarized by treatment group and visit using descriptive statistics. Changes or shifts from baseline will also be summarized where appropriate.

Summary of Known and Potential Risks and Benefits to Human Subjects

SkQ1 is a novel compound that has undergone extensive nonclinical evaluation in its ophthalmic solution formulation. Internationally, a total of 1005 patients have enrolled in clinical trials of SkQ1 ophthalmic solution conducted by Mitotech. Of these, approximately 559 patients have received SkQ1 ophthalmic solution and have post-dosing safety evaluations. The remainder received matching vehicle or did not have post-dosing safety information at the time this document was prepared.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]



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LIST OF ABBREVIATIONS

AE	adverse event
ANCOVA	Analysis of covariance
[REDACTED]	[REDACTED]
CFR	Code of Federal Regulations
CI	confidence interval
DES	Dry Eye Syndrome
DHHS	Department of Health and Human Services
eCRF	electronic case report form
EKG	electrocardiograph
ERC	ethical review committee
ETDRS	Early Treatment of Diabetic Retinopathy Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Information Portability and Accountability Act
ICF	informed consent form
ICH	International Conference on Harmonisation
IND	investigational new drug application
IOP	intraocular pressure
IRB	institutional/independent review board
ITT	intent-to-treat
IUD	intra uterine device
KCS	keratoconjunctivitis sicca
kg	kilogram
LASIK	laser <i>in situ</i> keratomileusis
logMAR	logarithm of the minimum angle of resolution
MedDRA	Medical Dictionary for Regulatory Activities
MGD	meibomian gland dysfunction
mL	milliliter
mm	millimeter
µg	microgram
mmHg	millimeters of mercury
OD	right eye
OS	left eye
OSDI	ocular surface disease index
OU	both eyes
OTC	over-the-counter
[REDACTED]	[REDACTED]
VA	visual acuity

1 INTRODUCTION

Dry eye syndrome (DES), also known as Keratoconjunctivitis sicca (KCS), is a multifactorial disease of the tears and ocular surface; symptoms include discomfort, visual disturbance, and tear film instability, with the potential for exposure of and damage to the ocular surface. The condition is accompanied by increased osmolarity of tears and inflammation of the ocular surface. Symptoms can be caused by defects in the aqueous, lipid, and/or mucin layers of the tear film¹. Current therapies for dry eye are only palliative, mostly focusing on replacement of tears to reduce symptoms. Only three approved products are available in the USA currently: Restasis® (Cyclosporine Ophthalmic Emulsion, Allergan, Irvine, California, USA), CEQUA™ (cyclosporine ophthalmic solution, Sun Pharma, Princeton, NJ, USA) and Xiidra® (lifitigrast ophthalmic solution, Shire US, Inc., Lexington, MA, USA).

Oxidative mechanisms are also believed to play an important role in the pathogenesis of age-related eye disease such as DES. Consequently, many investigations have focused on whether vitamins and trace minerals with antioxidant properties help prevent the onset or progression of DES.

SkQ1 is a novel compound and powerful antioxidant. Given its chemical properties, SkQ1 and related compounds have been shown to be active in a variety of animal models of illness believed to involve free radical damage. These include rat models of H₂O₂ and ischemia-induced heart arrhythmia, heart infarction, kidney ischemia, and stroke studied both ex vivo and in vivo.¹ In addition, SkQ1 has been found to provide benefit in a number of models of eye diseases, including DES²⁻⁶

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

2 STUDY OBJECTIVES

The objective of this study is to compare the safety and efficacy of SkQ1 ophthalmic solutions to placebo for the treatment of the signs and symptoms of DES.

3 CLINICAL HYPOTHESES

The clinical hypotheses for this study are that SkQ1 ophthalmic solution 1.55µg/mL and 0.155 µg/mL are superior to placebo for the primary endpoints of signs and symptoms, as follows:

- Subjects receiving SkQ1 ophthalmic solution will have a statistically significantly lower mean change from baseline (Visit 2) in central region corneal fluorescein staining score [REDACTED] at Visit 5 (Day 57) in the worst eye at baseline when compared to [REDACTED]
- Subjects receiving SkQ1 ophthalmic solution will have statistically significantly lower mean change from baseline (Visit 2) [REDACTED] at Visit 5 (Day 57) in grittiness score as determined from [REDACTED] Ocular Discomfort & 4-Symptom Questionnaire.

4 OVERALL STUDY DESIGN

See synopsis.

5 STUDY POPULATION

5.1 Number of Subjects (approximate)

It is estimated that approximately [REDACTED] subjects will be screened to enroll approximately 444 (148 high dose: 148 low dose: 148 placebo) subjects. Subjects will be randomized in a 1:1:1 ratio to 0.155 µg/mL SkQ1, 1.55 µg/mL SkQ1 or placebo.

5.2 Study Population Characteristics

All subjects must be at least 18 years of age, of either gender, and of any race, and must meet all inclusion criteria and none of the exclusion criteria.

5.3 Inclusion Criteria

Subjects must:

- a. Be at least 18 years of age;
- b. Provide written informed consent;
- c. Have a subject reported history of dry eye for at least 6 months prior to Visit 1;
- d. Have a history of use or desire to use eye drops for dry eye symptoms within 6 months of Visit 1;

e. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]


- k. Have at least one eye (the same eye) satisfy all criteria for f, g, h, i, and j above.

5.4 Exclusion Criteria

Subjects must not:

- a. Have participated in the previous SkQ1 ophthalmic solution Phase 2 treatment study;
- b. Have any clinically significant slit lamp findings at Visit 1 that may include active blepharitis, meibomian gland dysfunction (MGD), lid margin inflammation or active ocular allergies that require therapeutic treatment, and/or in the opinion of the investigator may interfere with study parameters;
- c. Be diagnosed with an ongoing ocular infection (bacterial, viral, or fungal), or active ocular inflammation (e.g. follicular conjunctivitis) at Visit 1;
- d. Have worn contact lenses within 7 days of Visit 1 or anticipate using contact lenses during the study;
- e. Have used any eye drops within 2 hours of Visit 1;
- f. Have previously had laser-assisted *in situ* keratomileusis (LASIK) surgery within the last 12 months;
- g. Have used Restasis[®], Xiidra[®] or CEQUA[™] within 60 days of Visit 1;
- h. Have had any ocular and/or lid surgeries within 6 months of Visit 1 or any planned over the study period;
- i. Be using or anticipate using temporary punctal plugs during the study that have not been stable within 30 days of Visit 1;
- j. Be currently taking any topical ophthalmic prescription (including medications for glaucoma) or over-the-counter (OTC) solutions, artificial tears, gels or scrubs, and cannot discontinue these medications for the duration of the trial (excluding medications allowed for the conduct of the study);
- k. Have corrected visual acuity greater than or equal to logMAR+0.7 as assessed by Early Treatment of Diabetic Retinopathy Study (ETDRS) scale in both eyes at Visit 1;
- l. Have an uncontrolled systemic disease;
- m. Be a woman who is pregnant, nursing or planning a pregnancy;
- n. Be unwilling to submit a urine pregnancy test at Visit 1 and Visit 5 (or early termination visit) if of childbearing potential. Non-childbearing

potential is defined as a woman who is permanently sterilized (e.g. has had a hysterectomy or bilateral tubal ligation or bilateral oophorectomy), or is post-menopausal (without menses for 12 consecutive months);

- o. Be a woman of childbearing potential who is not using an acceptable means of birth control; acceptable methods of contraception include: hormonal – oral, implantable, injectable, or transdermal contraceptives; mechanical – spermicide in conjunction with a barrier such as a diaphragm or condom; IUD; or surgical sterilization of partner. For non-sexually active females, abstinence may be regarded as an adequate method of birth control; however, if the subject becomes sexually active during the study, she must agree to use adequate birth control as defined above for the remainder of the study;
- p. 
- q. Have a condition or be in a situation which the investigator feels may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject's participation in the study;
- r. Be currently enrolled in an investigational drug or device study or have used an investigational drug or device within 30 days of Visit 1;
- s. Be currently using any medication known to cause ocular drying that is not used on a stable dosing regimen for at least 30 days prior to Visit 1;
- t. Be currently using any hormone replacement therapy that is not used on a stable dosing regimen for at least 30 days prior to Visit 1 and during the study;
- u. Be unable or unwilling to follow instructions, including participation in all study assessments and visits.

5.5 Withdrawal Criteria (if applicable)

If at any time during the study the investigator determines that a subject's safety has been compromised, the subject may be withdrawn from the study.

Subjects may withdraw consent from the study at any time.

Sponsor and/or investigator may discontinue any subject for non-compliance or any valid medical reason (see Section 8.6.2).

6 STUDY PARAMETERS

6.1 Efficacy Measures

6.1.1 Primary Efficacy Variables

The following primary endpoints will be tested:

- Change from baseline (Visit 2) in Corneal fluorescein staining in the central region at Visit 5 (Day 57) [REDACTED];
- Change from baseline (Visit 2) in Grittiness at Visit 5 (Day 57) [REDACTED], as measured by [REDACTED] Ocular Discomfort & 4-Symptom Questionnaire

6.1.2 Secondary Efficacy Variables

- [REDACTED]

6.1.3 Criteria for Effectiveness

The primary efficacy variables will be evaluated to assess effectiveness. For this phase 3 study, the primary analyses will each be evaluated at two-sided alpha levels of 0.05 (SkQ1 ophthalmic solution versus placebo) to determine evidence of efficacy. Testing will follow a hierarchical testing strategy, where efficacy for each endpoint and comparison to placebo will be determined only if the preceding test(s) are statistically significant.

6.2 Safety Measures

- Visual acuity (ETDRS);
- Slit-lamp biomicroscopy;
- Adverse event query;
- Dilated funduscopy;
- Intraocular pressure.

7 STUDY MATERIALS

7.1 Study Drug(s)

7.1.1 Run-In

Placebo SkQ1 ophthalmic solution (Vehicle of SkQ1 ophthalmic solution)

7.1.2 Study Drug(s)/ Formulation(s)

- 0.155 µg/mL SkQ1 ophthalmic solution
- 1.55 µg/mL SkQ1 ophthalmic solution
- Placebo SkQ1 ophthalmic solution (Vehicle)

7.1.3 Study Drug Packaging Configuration

Study drug will be contained in
clinical kit boxes.

7.1.4 Study Drug Storage and Accountability

The study drug must be stored in a secure area accessible only to the investigator and his/her designees. The study drug will be administered only to subjects entered into the clinical study, in accordance with the conditions specified in this protocol.

The study drug is to only be prescribed by the principal investigator or his/her named sub investigator(s), and is to only be used in accordance with this protocol. The study drug must only be distributed to subjects properly qualified under this protocol to receive study drug. The investigator must keep an accurate accounting of the study drug by maintaining a detailed inventory. This includes the amount of study drug

received by the site, amount dispensed to subjects, amount returned to the site by the subjects, and the amount returned to the Sponsor upon the completion of the study.

7.1.5 Instructions for Dispensation, Use, and Administration

At the end of Visit 1, qualified subjects will receive a kit [REDACTED]

At Visit 2, the run-in kit will be collected from subjects for drug accountability. At the end of Visit 2, qualified subjects will be randomized [REDACTED]

At Visit 3, the study drug kit will be collected from subjects for drug accountability. [REDACTED]

At Visit 4, the study drug kit will be collected from subjects for drug accountability. [REDACTED]

At Visits 5 the study drug kit will be collected from subjects for drug accountability. [REDACTED]

If needed, replacement kits are also available to be dispensed to a subject.

7.2 Other Study Supplies

Urine pregnancy tests, Schirmer's test strips, sodium fluorescein, lissamine green, tear collection supplies.



8.2 Concurrent Therapies

The use of any concurrent medication, prescription or over-the-counter, is to be recorded on the subject's source document and corresponding electronic case report form (eCRF) along with the reason the medication was taken.

Concurrent enrollment in another investigational drug or device study is not permitted.

8.2.1 Prohibited Medications/Treatments

Disallowed medications/treatments during the study are outlined in the Exclusion Criteria (Section 5.4).

8.2.2 Escape Medications

No escape medications are required for this study.

8.2.3 Special Diet or Activities

No special diets or activities are required for this study.

8.3 Examination Procedures

8.3.1 Procedures to be Performed at Each Study Visit with Regard to Study Objective(s)

The following procedures will be performed (see Appendix 2 for description):

Visit 1 (Day -7 ±1): Environmental Screening

- Informed consent / HIPAA;
- Demographic data and medical / medication history;
- Urine pregnancy test (for females of childbearing potential);
- [REDACTED] Ocular Discomfort Scale;
- [REDACTED] Ocular Discomfort Scale & 4-Symptom Questionnaire;
- [REDACTED]
- Visual acuity;

- Collection and review of run-in (RUN-IN) [REDACTED];
- [REDACTED]
- Medical/medication history update;
- Adverse event query;
- [REDACTED] Ocular Discomfort Scale;
- [REDACTED] Ocular Discomfort Scale & 4-Symptom Questionnaire;
- [REDACTED]
- Visual acuity;
- Review of qualification criteria;
- Slit-lamp biomicroscopy;
- [REDACTED]
- [REDACTED]
- TFBUT;
- Fluorescein staining [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- Review of qualification criteria;
- Randomization;
- Dispensation of study drug kit according to randomization for [REDACTED]
[REDACTED] until Visit 3;
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

- [REDACTED]
 - [REDACTED]
 - [REDACTED]
 - [REDACTED]
- Adverse event query;
- Schedule subjects for Visit 3.

Visit 3 (Day 29 ± 2): 2-Week Follow-Up

- Collection and review of study drug [REDACTED]
- [REDACTED]
- Medical / medication history update;
- Adverse event query;
- [REDACTED] Ocular Discomfort Scale;
- [REDACTED] Ocular Discomfort Scale & 4-Symptom Questionnaire;
- [REDACTED]®;
- Visual acuity;
- Slit-lamp biomicroscopy;
- [REDACTED]
- [REDACTED]
- TFBUT;
- Fluorescein staining [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- Dispensation of study drug kit according to randomization for [REDACTED]
[REDACTED] until Visit 4;
- [REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]
 - [REDACTED]
 - [REDACTED]
 - [REDACTED]
- Adverse event query;
- Schedule subjects for Visit 4.

Visit 4 (Day 43 ± 2): 4-Week Follow-up

- Collection and review of study drug [REDACTED];
- [REDACTED]
- Medical / medication history update;
- Adverse event query;
- [REDACTED] Ocular Discomfort Scale;
- [REDACTED] Ocular Discomfort Scale & 4-Symptom Questionnaire;
- [REDACTED]
- Visual acuity;
- Slit-lamp biomicroscopy;
- [REDACTED]
- [REDACTED]
- TFBUT;
- Fluorescein staining [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- Adverse event query;
- Schedule subjects for Visit 5.

Visit 5 (Day 57 ± 4): 8-Week CAE® Challenge/ End of Double-Masked Treatment

- Collection and review of study drug [REDACTED]
- Medical / medication history update;
- Adverse event query;
- Urine pregnancy test (for females of childbearing potential);
- [REDACTED] Ocular Discomfort Scale;
- [REDACTED] Ocular Discomfort Scale & 4-Symptom Questionnaire;
- [REDACTED]
- Visual acuity;
- Slit-lamp biomicroscopy;
- [REDACTED]
- [REDACTED]
- TFBUT;
- Fluorescein staining [REDACTED]
- [REDACTED]
- [REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- Slit-lamp biomicroscopy;
- [REDACTED]
- [REDACTED]
- TFBUT;
- Fluorescein staining [REDACTED]
- [REDACTED]
- Intraocular pressure;
- Dilated funduscopy;
- Adverse event query;
- Study Exit.

Early Termination/Discontinuation

If a subject is discontinued from the study prior to Visit 5 (Day 57 \pm 4), then all safety evaluations [REDACTED] that are to be performed at Visit 5 should be performed on the day of discontinuation (early termination) or at the discretion of the investigator.

Adverse Events (both elicited and observed) and SAEs will be monitored throughout the study. The investigator will promptly review all adverse events (both elicited and observed) for accuracy and completeness. All adverse events will be documented on the appropriate source document and eCRF.

If a female reports a pregnancy or has a positive pregnancy test during the study, then the investigator will notify Ora immediately. The investigator shall instruct the patient to immediately stop the study medication and request from the subject and/or the subject's physician copies of all related medical reports during the pregnancy and shall document the outcome of the pregnancy. The investigator will retain these reports together with the

subject's source documents and will provide a copy of all documentation to Ora.

8.4 Schedule of Visits, Measurements and Dosing

8.4.1 Scheduled Visits

Refer to Appendix 1 for a schedule of visits and measurements.

8.4.2 Unscheduled Visits

These visits may be performed in order to ensure subject safety. All procedures performed at an unscheduled visit will be recorded in the source documents and on the Unscheduled Visit eCRF pages. Any procedure indicated in the eCRF that is not performed should be indicated as "Not done."

Evaluations that may be conducted at an Unscheduled Visit include:

- Slit-lamp Biomicroscopy;
- Visual Acuity;
- Intraocular Pressure;
- Pregnancy Test;
- Dilated Fundoscopy;
- Assessment of Adverse Events;
- Assessment of concomitant medications and/or treatments; and
- Any other assessments needed in the judgment of the investigator.

8.5 Compliance with Protocol

Subjects will be instructed on proper [REDACTED] instillation and storage of study drug at the end of Visits 1, 2, 3, and 4 and given written instructions. [REDACTED]

8.6 Subject Disposition

8.6.1 Completed Subjects

A completed subject is one who has not been discontinued from the study.

8.6.2 Discontinued Subjects

Subjects may be discontinued prior to their completion of the study due to:

- adverse events;
- protocol violations;
- administrative reasons (e.g., inability to continue due to scheduling changes);
- lost to follow up;
- sponsor termination of study;
- subject choice (e.g. withdrawal of consent); and
- other

Note: In addition, any subject may be discontinued for any sound medical reason at the discretion of the investigator.

Notification of a subject discontinuation and the reason for discontinuation will be made to Ora and/or study sponsor and will be clearly documented on the eCRF.

8.7 Study Termination

The study may be stopped at any time by the investigator, the sponsor, and/or Ora with appropriate notification.

8.8 Study Duration

An individual subject's participation will involve 5 visits over approximately a 9-week period (63 days).

8.9 Monitoring and Quality Assurance

During the course of the study a monitor, or designee, will make routine site visits to review protocol compliance, assess study drug accountability and storage conditions, subject safety, and ensure the study is being conducted according to the pertinent regulatory requirements. The review of the subjects' medical records will be performed in a manner that adequately maintains subject confidentiality. Further details of the study monitoring will be outlined in a monitoring plan.

Regulatory authorities of domestic and foreign agencies, Ora, Inc. quality assurance, the sponsor and/or its designees may carry out on-site inspections and/or audits, which may include source data checks. Therefore direct access to the original source data will be required for inspections and/or audits. All inspections and audits will be

carried out giving consideration to data protection as well as subject confidentiality to the extent that local, state, and federal laws apply.

9 ADVERSE EVENTS

9.1 Adverse Event

An adverse event is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not the event is considered drug-related. An adverse event can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease occurring after the subject started dosing with the study drug, without any judgment about causality. Any pre-existing medical condition that worsens after administration of the study drug will also be considered a new adverse event.

If there is a worsening of a medical condition that was present prior to the administration of the study drug, this should also be considered a new adverse event and reported. Any medical condition present prior to the administration of the study drug that remains unchanged or improved should not be recorded as a treatment emergent adverse event at subsequent visits unless it worsens during treatment.

Study drug includes the investigational drug under evaluation and any comparator drug, placebo, or any other medications required by the protocol given during any stage of the study.

Documentation regarding the adverse event should be made as to the nature, date of onset, end date, severity, relationship to study drug, action(s) taken, seriousness, and outcome of any sign or symptom observed by the physician or reported by the patient upon indirect questioning.

9.1.1 Severity

Severity of an adverse event is defined as a qualitative assessment of the degree of intensity of an adverse event as determined by the investigator or reported to him/her by the patient/subject. The assessment of severity is made irrespective of relationship to study drug or seriousness of the event and should be evaluated according to the following scale:

- *Mild*: Event is noticeable to the subject, but is easily tolerated and does not interfere with the subject's daily activities.
- *Moderate*: Event is bothersome, possibly requiring additional therapy, and may interfere with the subject's daily activities.
- *Severe*: Event is intolerable, necessitates additional therapy or alteration of therapy, and interferes with the subject's daily activities.

9.1.2 Relationship to Study Drug

The relationship of each adverse event to the study drug should be determined by the investigator using these explanations:

- *Definite*: When there are good reason and sufficient documentation to demonstrate a direct causal relationship between investigational product and AE;
- *Probable*: When there are good reasons and sufficient documentation to assume a causal relationship in the sense of plausible, conceivable, likely but not necessarily highly probable.
- *Possible*: When there is sufficient information to accept the possibility of a causal relationship in the sense of not impossible and not unlikely, although the connection is uncertain or doubtful, for example, due to missing data or insufficient evidence.
- *None*: When there is sufficient information to accept a lack of a causal relationship, in the sense of impossible and improbable.
- *Unclassified*: When the causal relationship is not assessable for whatever reason due to insufficient evidence, conflicting data or poor documentation.

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the study drug caused the adverse event. “Reasonable possibility” means there is evidence to suggest a causal relationship between the study drug and the adverse event. Types of evidence that would suggest a causal relationship between the study drug and the adverse event include: a single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome); one or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture); an aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

9.1.3 Expectedness

The expectedness of an adverse event should be determined based upon existing safety information about the study drug using these explanations:

- *Unexpected*: An adverse event that is not listed in the Investigator’s brochure or is not listed at the specificity or severity that has been observed.
- *Expected*: An adverse event that is listed in the Investigator’s brochure at the specificity and severity that has been observed.

- *Not Applicable*: Any adverse event that is unrelated to the study drug.

Adverse events that are mentioned in the Investigator's brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation are to be considered unexpected.

The investigator should initially classify the expectedness of an adverse event, but the final classification is subject to the Medical Monitor's determination.

9.2 Serious Adverse Events

An adverse event is considered serious if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death;
- A life-threatening adverse event;

Note: An adverse event is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death.

- Inpatient hospitalization or prolongation of existing hospitalization;

Note: The term "inpatient hospitalization" refers to any inpatient admission (even if less than 24 hours). For chronic or long-term inpatients, inpatient admission includes transfer within the hospital to an acute/intensive care inpatient unit. Inpatient hospitalization does not include: emergency room visits; outpatient/same-day/ambulatory procedures; observation/short stay units; rehabilitation facilities; hospice facilities; nursing homes; or clinical research/phase 1 units.

Note: The term "prolongation of existing hospitalization" refers to any extension of an inpatient hospitalization beyond the stay anticipated or required for the reason for the initial admission as determined by the investigator or treating physician.

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;

Note: A serious adverse event specifically related to visual threat would be interpreted as any potential impairment or damage to the subject's eyes (e.g., hemorrhage, retinal detachment, central corneal ulcer or damage to the optic nerve).

- A congenital anomaly/birth defect.

Important medical events that may not result in death, are life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

9.3 Procedures for Reporting Adverse Events

All adverse events and their outcomes must be reported to Ora, the study sponsor, and the IRB as required by the IRB, federal, state, or local regulations and governing health authorities and recorded on the appropriate eCRF.

9.3.1 Reporting a Suspected Unexpected Adverse Reaction

All adverse events that are ‘suspected’ and ‘unexpected’ are to be reported to Ora, the study sponsor and the IRB as required by the IRB, federal, state, or local regulations and governing health authorities.

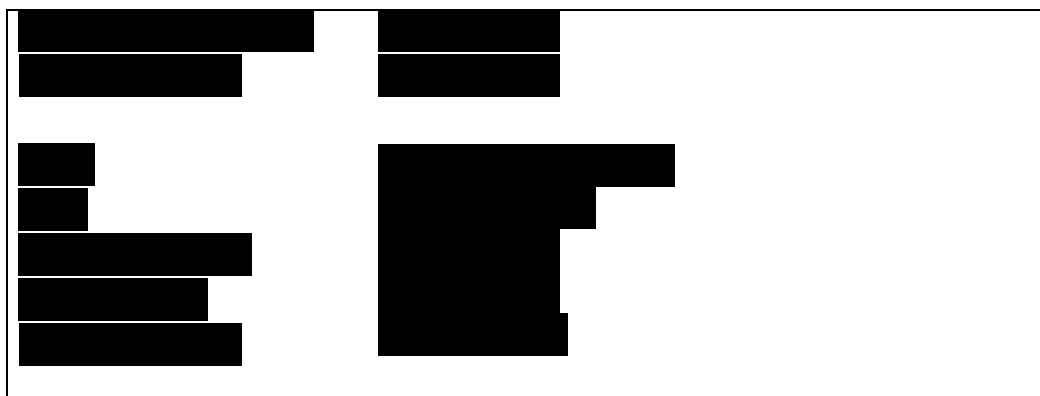
9.3.2 Reporting a Serious Adverse Event

To ensure subject safety, all serious adverse events, regardless of relationship to the study drug, must be immediately reported. All information relevant to the serious adverse event must be recorded on the appropriate eCRF. The investigator is obligated to pursue and obtain information requested by Ora and/or the sponsor in addition to that information reported on the eCRF. All subjects experiencing a serious adverse event must be followed up and the outcome reported.

In the event of a serious adverse event, the investigator must notify Ora and the sponsor immediately (within 24 hours); obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the subject; provide Ora and the study sponsor with a complete case history, which includes a statement as to whether the event was or was not suspected to be related to the use of the study drug; and inform the IRB of the adverse event within their guidelines for reporting serious adverse events.

Serious adverse events should be reported within one day to the contacts listed below:

[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]



9.4 Procedures for Unmasking of Study Drug

All subjects, investigators, and study personnel involved with the conduct of the study will be masked with regard to treatment assignments. When medically necessary, the investigator may need to determine what treatment arm has been assigned to a subject. When possible (i.e., in non-emergent situations), Ora and/or the study sponsor should be notified before unmasking study drug.

If an investigator identifies a medical need for unmasking the treatment assignment of a subject, he/she should contact Ora and/or the medical monitor prior to unmasking the identity of the IP, if possible. Ora will ask the site to complete and send them the Unmasking Request Form. Ora will notify Mitotech and jointly will determine if the unmasking request should be granted. They may consult the medical monitor as needed. The result of the request will be documented on the Unmasking Request Form. If approval is granted to unmask a subject, written permission via the Unmasking Request Form will be provided to the investigator. The investigator will unmask the subject [REDACTED]. The investigator will complete the Unmasking Memo form and include it in the subject's study file and provide a copy for the Trial Master File (TMF). For each unmasked request, the reason, date, signature, and name of the person who unmasked the subject, must be noted in the subject's study file.

9.5 Type and Duration of the Follow-up of Subjects after Adverse Events

Adverse events that are ongoing at the end of the study visit will be followed. Phone calls will be placed with any subject who experiences an adverse event until the issue is resolved or the condition is considered ongoing and stable.

10 STATISTICAL HYPOTHESES AND METHODS OF ANALYSES

10.1 Analysis Populations

Intent-to-Treat Population – The intent-to-treat (ITT) population includes all randomized subjects. The primary and secondary efficacy analyses will be performed

on the ITT population. Subjects in the ITT population will be analyzed as randomized.

Per-Protocol Population – The per protocol (PP) population excludes subjects with significant protocol deviations or who do not complete the study. Protocol deviations will be assessed and the Per-protocol population identified prior to database lock and unmasking. Subjects in the PP population will be analyzed as treated.

Safety Population – The safety population will include all subjects receiving treatment from whom at least one safety measurement is obtained following the first dose of study drug. The safety population will be analyzed for all safety assessments. Subjects in the Safety population will be analyzed as treated.

The statistical analysis of safety data will be performed for the safety population. The analysis of baseline and efficacy data will be performed for the ITT population. The primary efficacy analysis will also be performed on the PP population for sensitivity analysis.

10.2 Statistical Hypotheses

The following statistical hypotheses will be tested, with H_{01} , H_{02} , H_{03} , and H_{04} tested (in that order) comparing SkQ1 ophthalmic solution versus placebo. Each hypothesis test will be conditional upon the prior test(s) rejecting the null hypothesis. The statistical hypotheses are stated in terms of one-sided hypotheses, although statistical testing will be two-sided. Each test is therefore successful with respect to efficacy if the corresponding null hypothesis is rejected using a two-sided significance level of 0.05.

H_{01} : There is no difference between SkQ1 0.155 $\mu\text{g/mL}$ ophthalmic solution and placebo for the change from baseline in corneal fluorescein staining in the central region [REDACTED] at Visit 5 (Day 57), [REDACTED].

H_{11} : The change from baseline in corneal fluorescein staining in the central region [REDACTED] at Visit 5 (Day 57), [REDACTED], is less with SkQ1 0.155 $\mu\text{g/mL}$ ophthalmic solution than with placebo.

H_{02} : There is no difference between SkQ1 0.155 $\mu\text{g/mL}$ ophthalmic solution and placebo for the change from baseline in grittiness [REDACTED] at Visit 5 (Day 57), using [REDACTED] Ocular Discomfort & 4-Symptom Questionnaire.

H_{12} : The change from baseline in grittiness [REDACTED] at Visit 5 (Day 57), using [REDACTED] Ocular Discomfort & 4-Symptom Questionnaire, is less with SkQ1 0.155 $\mu\text{g/mL}$ ophthalmic solution than with placebo.

H_{03} : There is no difference between SkQ1 1.55 $\mu\text{g/mL}$ ophthalmic solution and placebo for the change from baseline in corneal fluorescein staining in the central region [REDACTED] at Visit 5 (Day 57), [REDACTED].

H₁₃: The change from baseline in corneal fluorescein staining in the central region [REDACTED] at Visit 5 (Day 57), [REDACTED], is less with SkQ1 1.55 µg/mL ophthalmic solution than with placebo.

H₀₄: There is no difference between SkQ1 1.55 µg/mL ophthalmic solution and placebo for the change from baseline in grittiness [REDACTED] at Visit 5 (Day 57), using [REDACTED] Ocular Discomfort & 4-Symptom Questionnaire.

H₁₄: The change from baseline in grittiness [REDACTED] at Visit 5 (Day 57), using [REDACTED] Ocular Discomfort & 4-Symptom Questionnaire, is less with SkQ1 1.55 µg/mL ophthalmic solution than with placebo.

10.3 Sample Size

To address the multiple primary efficacy variables employed in this study, the sample size calculations have been based on a hierarchical structure. In order to test a variable, the preceding variable(s) must have shown statistically significant improvements versus placebo using a two-sided significance level of 0.05. Using these strategies, the Type I error rate will be maintained at the 0.05 significance level for the primary efficacy variables.

This study is expected to enroll 148 subjects in each of the active treatment arms and 148 subjects in the placebo arm. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED], enrollment of 148 patients per group would be required for 90% power to detect the differences between each active group and placebo.

10.4 Statistical Analysis

10.4.1 General Considerations

The quantitative variables will be summarized using mean, median, standard deviation (SD), minimum and maximum. The qualitative variables will be summarized using counts and percentages.

All efficacy analyses will be evaluated at a two-sided $\alpha = 0.05$ and two-sided 95% CIs around the difference between treatments (SkQ1 – placebo) as well as two-sided 95% CIs around the point estimates within each treatment group.

All summaries will be presented by treatment group. Summaries will be provided for demographics, baseline medical history, and subject disposition.

Baseline measures are defined as the last measure prior to the initiation of study treatment (Visit 2). [REDACTED]

10.4.2 Unit of Analysis

Safety endpoints will be analyzed for both eyes. For efficacy endpoints collected at the eye level, the unit of analysis will be the “worst eye” [REDACTED]

[REDACTED]

10.4.3 Missing Data

The primary efficacy analyses will be performed using Markov Chain Monte Carlo multiple imputation to account for missing Day 57 data. [REDACTED]

[REDACTED]

In order to show that the primary results are robust to various patterns of missing data, sensitivity models will include the following methods of handling missing data for each primary endpoint:

- Using a control-based pattern mixture for multiple imputation

- Using the last observation carried forward (LOCF) method for missing values
- Analyzing observed data only
- Analyzing observed data for the PP population

Imputation will not be applied for any missing data in the secondary efficacy endpoints.

10.4.4 Multiplicity Adjustments

The primary efficacy analyses will be tested following a hierarchical testing strategy in order to maintain a study-wide type I error rate of 0.05 while testing the primary hypotheses. The testing strategy will proceed as follows:

- 1) Compare the change from baseline in [REDACTED] central corneal staining at Day 57 between SkQ1 0.155 µg/mL and placebo. If statistically significant at a two-sided alpha = 0.05, proceed to step 2; otherwise no further testing will be performed and all other testing is considered exploratory.
- 2) Compare the change from baseline in [REDACTED] grittiness at Day 57 between SkQ1 0.155 µg/mL and placebo. If statistically significant at a two-sided alpha = 0.05, proceed to step 3; otherwise no further testing will be performed and all other testing is considered exploratory.
- 3) Compare the change from baseline in [REDACTED] central corneal staining at Day 57 between SkQ1 1.55 µg/mL and placebo. If statistically significant at a two-sided alpha = 0.05, proceed to step 4; otherwise no further testing will be performed and all other testing is considered exploratory.
- 4) Compare the change from baseline in [REDACTED] grittiness at Day 57 between SkQ1 1.55 µg/mL and placebo. All other testing is considered exploratory.

10.4.5 Primary Efficacy Analyses

Efficacy analyses will be performed on the ITT population. Supportive analyses will be performed on the PP population.

Primary efficacy endpoints are:

- Corneal fluorescein staining in the central region, change from baseline [REDACTED] at Visit 5 (Day 57), [REDACTED] in the worst eye at baseline;
- Grittiness, change from baseline [REDACTED] at Visit 5 (Day 57), as measured by [REDACTED] Ocular Discomfort & 4-Symptom Questionnaire

The primary efficacy endpoints will be analyzed using an analysis of covariance (ANCOVA) model. [REDACTED]. The [REDACTED]. The adjusted least squares means and their standard errors (SEs) will be presented along with their two-sided 95% confidence intervals (CIs) for each treatment group and the difference between the active treatment group and the placebo treatment group. In addition, a two-sample t-test and Wilcoxon rank sum test will be used to compare the active and placebo groups in the change from baseline at Visit 5 [REDACTED]. The mean difference, SD for the difference, and the 95% CI for the difference will be presented. A two-sided p-value < 0.05 will be considered statistically significant.

10.4.6 Secondary Efficacy Variables

Secondary efficacy variables will generally be analyzed on the ITT population using observed data. Where appropriate, the study eye will be the unit of analysis. Analyses will use two-sample t-tests, Wilcoxon rank sum tests (for count or rank-based data, including symptom scores at individual time points), and ANCOVA models with baseline values included as covariates where appropriate. [REDACTED]

10.4.7 Safety Variables

Adverse events will be coded using the MedDRA dictionary.

Frequencies and percentages of subjects with treatment-emergent adverse events (TEAEs), serious TEAEs, and TEAEs causing premature treatment discontinuation will be provided by treatment group. An AE is treatment emergent if it occurs or worsens after the first dose of study treatment. Furthermore, frequencies will be given of subjects with TEAEs by system organ class and preferred term for the following categories of AEs:

- All TEAEs
- TEAEs at least possibly related to study treatment
- TEAEs leading to study treatment discontinuation
- Serious TEAEs
- By maximal severity
- By study day of onset

Separate analyses will be performed for ocular and non-ocular AEs.

Other safety endpoints will be summarized by treatment group and visit using descriptive statistics. Changes or shifts from baseline will also be summarized where appropriate.

10.4.8 Interim Analyses

There will be no interim analyses.

11 COMPLIANCE WITH GOOD CLINICAL PRACTICES, ETHICAL CONSIDERATIONS, AND ADMINISTRATIVE ISSUES

This study will be conducted in compliance with the protocol, Good Clinical Practices (GCPs), including the International Conference on Harmonization (ICH) Guidelines, and in general, consistent with the Declaration of Helsinki. In addition, all applicable local, state, and federal requirements relevant to the use of study drugs in the countries involved will be adhered to.

11.1 Protection of Human Subjects

11.1.1 Subject Informed Consent

Informed consent/assent must take place before any study specific procedures are initiated. Signed and dated written informed consent must be obtained from each subject prior to enrollment into the study.

All informed consent forms must be approved for use by the sponsor and receive approval/favorable opinion from an IRB prior to their use. If the consent form requires revision (e.g., due to a protocol amendment or significant new safety information), it is the investigator's responsibility to ensure that the amended informed consent is reviewed and approved by Ora prior to submission to the governing IRB and that it is read, signed and dated by all subjects subsequently enrolled in the study as well as those currently enrolled in the study.

11.1.2 Institutional Review Board (IRB) Approval

This study is to be conducted in accordance with Institutional Review Board regulations (U.S. 21 CFR Part 56.103). The investigator must obtain appropriate IRB approval before initiating the study and re-approval at least annually.

Only an IRB approved version of the informed consent form will be used.

11.2 Ethical Conduct of the Study

This study will be conducted in accordance with the ethical principles that originated with the Declaration of Helsinki.

11.3 Subject Confidentiality

All personal study subject data collected and processed for the purposes of this study should be maintained by the investigator and his/her staff with adequate precautions as to ensure that the confidentiality of the data in accordance with local, state, and federal laws and regulations.

Monitors, auditors and other authorized representatives of Ora, the sponsor, the IRB approving this study, the FDA, the DHHS, other domestic government agencies, and other foreign regulatory agencies will be granted direct access to the study subject's original medical and study records for verification of the data and/or clinical trial procedures. Access to this information will be permitted to the aforementioned individuals to the extent permitted by law.

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the study drug may ultimately be marketed, but the subject's identity will not be disclosed in these documents.

11.4 Documentation

Source documents may include a subject's medical records, hospital charts, clinic charts, the investigator's study subject files, as well as the results of diagnostic tests such as X-rays, laboratory tests, and EKGs. The investigator's copy of the eCRF serves as the investigator's record of a subject's study-related data.

11.4.1 Retention of Documentation

All study-related source documents, correspondence, patient records, consent forms, record of the distribution and use of all study drug and copies of case report forms should be maintained on file for at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region; or until at least two years have elapsed since the formal discontinuation of clinical development of the study drug. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian.

11.5 Labeling, Packaging, Storage, Accountability, and Return or Disposal of Study Drug

11.5.1 Labeling/Packaging

[REDACTED]

All run-in and study drug will be labeled according to applicable regulatory requirements.

11.5.2 Storage of Study Drug

The study drug must be stored in a secure area accessible only to the investigator and his/her designees. The study drug will be administered only to subjects entered into the clinical study, in accordance with the conditions specified in this protocol.

[REDACTED]

11.5.3 Accountability of Study Drug

The study drug is to only be prescribed by the principal investigator or his/her named sub investigator(s), and is to only be used in accordance with this protocol. The study drug must only be distributed to subjects properly qualified under this protocol to receive study drug. The investigator must keep an accurate accounting of the study drug by maintaining a detailed inventory. This includes the amount of study drug received by the site, amount dispensed to subjects, amount returned to the site by the subjects, and the amount returned to the Sponsor upon the completion of the study.

11.5.4 Return or Disposal of Study Drug

All study drug will be returned to the sponsor or their designee or destroyed on behalf of the Sponsor following local regulations.

11.6 Recording of Data on Source Documents and electronic Case Reports Forms (eCRFs)

The investigator is responsible for ensuring that study data is completely and accurately recorded on each subject's eCRF, source document, and all study-related material. All study data should also be attributable, legible, contemporaneous, and original. Recorded datum should only be corrected in a manner that does not obliterate, destroy, or render illegible the previous entry (e.g., by drawing a single line

through the incorrect entry and writing the revision next to the corrected data). An individual who has corrected a data entry should make clear who made the correction and when, by adding to the correction his/her initials as well as the date of the correction

11.7 Handling of Biological Specimens

Tear samples will be submitted to one or more central laboratories and/or analytical laboratories for processing, storage and analysis. All laboratories meet Good Laboratory Practice requirements.

11.1 Publications

Authorship and manuscript composition will reflect cooperation among all parties involved in the study. Authorship will be established before writing the manuscript. Ora and the study sponsor will have the final decision regarding the manuscript and publication.

12 REFERENCES

1. Bakeeva LE, Barskov IV, Egorov MV, et al. Mitochondria-targeted plastoquinone derivatives as tools to interrupt execution of the aging program. 2. Treatment of some ROS- and age-related diseases (heart arrhythmia, heart infarctions, kidney ischemia, and stroke). *Biochemistry Biokhimiia* 2008;73:1288-99.
2. Markovets AM, Fursova AZ, Kolosova NG. Therapeutic action of the mitochondria-targeted antioxidant SkQ1 on retinopathy in OXYS rats linked with improvement of VEGF and PEDF gene expression. *PloS one* 2011;6:e21682.
3. Neroev VV, Archipova MM, Bakeeva LE, et al. Mitochondria-targeted plastoquinone derivatives as tools to interrupt execution of the aging program. 4. Age-related eye disease. SkQ1 returns vision to blind animals. *Biochemistry Biokhimiia* 2008;73:1317-28.
4. Saprunova VB, Lelekova MA, Kolosova NG, Bakeeva LE. SkQ1 slows development of age-dependent destructive processes in retina and vascular layer of eyes of wistar and OXYS rats. *Biochemistry Biokhimiia* 2012;77:648-58.
5. Saprunova VB, Pilipenko DI, Alexeevsky AV, Fursova A, Kolosova NG, Bakeeva LE. Lipofuscin granule dynamics during development of age-related macular degeneration. *Biochemistry Biokhimiia* 2010;75:130-8.
6. Snytnikova OA, Tsentalovich YP, Stefanova NA, et al. The therapeutic effect of mitochondria-targeted antioxidant SkQ1 and *Cistanche deserticola* is associated with increased levels of tryptophan and kynurenine in the rat lens. *Doklady Biochemistry and biophysics* 2012;447:300-3.
7. Skulachev VP. What is "phenoptosis" and how to fight it? *Biochemistry Biokhimiia* 2012;77:689-706.

